

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Cymoxanil

Chemical Code # 4002, Tolerance # 52067  
SB 950 # NA

April 9, 2004

I. DATA GAP STATUS

<b>Chronic toxicity, rat:</b>	No data gap, no adverse effects
<b>Chronic toxicity, dog:</b>	No data gap, no adverse effects
<b>Oncogenicity, rat:</b>	No data gap, no adverse effects
<b>Oncogenicity, mouse:</b>	No data gap, possible adverse effect, non-oncogenic
<b>Reproduction, rat:</b>	No data gap, no adverse effects
<b>Teratology, rat:</b>	No data gap, no adverse effects
<b>Teratology, rabbit:</b>	No data gap, possible adverse effect
<b>Gene mutation:</b>	No data gap, no adverse effects
<b>Chromosome effects:</b>	No data gap, no adverse effects
<b>DNA damage:</b>	No data gap, no adverse effect
<b>Neurotoxicity:</b>	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 207331 were examined.

\*\* indicates an acceptable study.

Bold face indicates a possible adverse effect.

## indicates a study on file but not yet reviewed.

File name: T040409

Revised by Thomas Moore, 4/9/04

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

\*\* 029; 139826; "Combined Chronic Toxicity/Oncogenicity Study with DPX-T3217-113 (Cymoxanil) Two-Year Feeding Study in Rats" (L.R. Cox, E.I. du Pont de Nemours & Co., Haskell Lab. for Toxicology & Industrial Medicine, Newark, DE, Report # 678-93, 8/18/94); DPX-T3217-113 (96.5% a.i.) administered in diet to 72 rats/sex/dose at 0, 50, 100, 700, or 2000 ppm for 23 months (mean intake of DPX-T3217-113: males - 0, 1.98, 4.08, 30.3, and 90.1 mg/kg/day, respectively; females - 0, 2.71, 5.36, 38.4, and 126 mg/kg/day, respectively); study was terminated at 23 months due to poor survival in males and females; overall survival was 26, 29, 24, 45 and 34% for males, respectively, and 21, 34, 34, 27 and 40% for females, respectively; reduced mean body weight/body weight gain without any changes in food consumption was reported in 700 ppm males and 2000 ppm animals; incidence of male rats with masses in the 2000 ppm group falls within the range of historical control and is therefore, not considered to be toxicologically significant; **possible adverse effects**; histopathological exam revealed: increased incidence of retinal atrophy in 700 and 2000 ppm animals, sciatic nerve axon/myelin degeneration in 700 and 2000 ppm females without any indications of peripheral neuropathy, elongate spermatid degeneration in the testes of the 700 and 2000 ppm males, and polyarteritis and inflammation in 1 or more organs in 700 and 2000 ppm females and 2000 ppm males; NOEL (M/F) = NOAEL (M/F) = 100 ppm (based on abnormal histopathological changes as described above); **acceptable**; (Leung, 9/14/95)

### CHRONIC TOXICITY, RAT

See Combined Rat above.

### CHRONIC TOXICITY, DOG

\*\* 023; 139839; "Chronic Toxicity Study with DPX-T3217-113 (Cymoxanil) One Year Feeding Study in Dogs" (E. C. Tompkins, WIL Research Lab., Inc., Ashland, OH, Lab. Project ID # WIL-189003, 4/6/94); DPX-T3217-113 (97.8% a.i.) administered in diet to 5 beagle dogs/sex/dose at 0, 25 (F only), 50, 100, and 200 (M only) ppm for 52 weeks; average test article consumption - M: 0, 1.8, 3.0, and 5.7 mg/kg/day, respectively; F: 0, 0.7, 1.6, and 3.1 mg/kg/day, respectively; all animals survived the study until scheduled termination; no test article related clinical signs were observed at any concentration; males and females from the high dose groups experienced body weight loss due to reduced food consumption during the first week of the study but recovered fully by the end of the study and was not considered to be toxicologically significant; no treatment-related changes in hematology, clinical chemistry, urinalysis, ophthalmology, organ weights, macroscopic and microscopic pathology were detected; **no adverse effects**; NOEL (M) = 200 ppm, (F) = 100 ppm (no effect at HDT); NOAEL (M) > 200 ppm, (F) > 100 ppm; **acceptable**; (Leung, 9/8/95).

### ONCOGENICITY, RAT

See Combined Rat above.

### ONCOGENICITY, MOUSE

\*\* 024; 139841; "Oncogenicity Study with DPX-T3217-113 (Cymoxanil) Eighteen-Month Feeding Study in Mice" (L.R. Cox, E.I. du Pont de Nemours & Co., Haskell Lab. for Toxicology & Industrial Medicine, Newark, DE, Haskell Report # 667-93, 7/6/94); DPX-T3217-113 (97.8% a.i.) administered in diet to 90 mice/sex/dose at 0, 30, 300, 1500, or 3000 ppm for 18 months; female mice in the high dose group exhibited a significant decrease in survival; overall survival was 67, 70, 78, 65 and 73% for males, respectively, and 69, 76, 78, 74 and 57% for females, respectively; reduced body weight was not accompanied by any changes in food consumption; **possible adverse effects (not oncogenic)**: histopathological exam revealed increased incidences of lesions consisting of centrilobular apoptotic hepatocytes, pigment containing macrophages and granuloma in 300 ppm males and in 1500 and 3000 ppm animals; other abnormal changes noted

were bilateral testicular atrophy along with epididymal oligospermia and sperm cyst/cystic dilatation, sperm granuloma, and/or tubular dilatation males treated at doses  $\geq$  300 ppm; necrosis of the pancreatic acinar cells in two 3000 ppm females which were sacrificed in moribund condition during the first 2 weeks of the study; three other 3000 ppm females were observed to have pancreatic acinar cell necrosis which were sacrificed within 35 days of dosing; increased incidence of hyperplastic gastropathy (300, 1500, and 3000 ppm females) and cystic enteropathy in the duodenum and/or jejunum (300 females and 1500 and 3000 ppm animals) were detected; NOAEL (M/F) = NOEL (M/F) = 30 ppm (based on hepatotoxicity and testicular atrophy in males and toxicity of the GI tract in females); **acceptable**; (Leung, 9/12/95)

#### REPRODUCTION, RAT

\*\* 025; 139801; "Reproductive and Fertility Effects with DPX-T3217-113 (Cymoxanil) Multigeneration Reproduction Study in Rats", (M.E. Hurtt; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 568-93; 12/21/93); Cymoxanil Technical (DPX-T3217-113; purity:  $\geq$  96.5%); 30 animals/sex/group, multigeneration; Doses: 0, 100, 500, 1500 ppm, in the diet; **Parental-Mortality**: 8 F1 females in the 1500 ppm treatment group died or euthanized *in extremis*; Clinical Observations: lower body weight (M,F; P1, F1 generations, 1500 ppm), reduced food consumption (M,F; P1, F1 generations, 1500 ppm); Necropsy and Histopathology: mastitis (F; F1 generation, 1500 ppm); **Offspring**-reduced litter size (F1 litters, 1500 ppm), reduced mean pup weight during lactation (all litters, 1500 ppm, F2B litter, 500 ppm), reduced viability index (F1 litter, 1500 ppm); **no adverse effects**; **Parental NOAEL**: 500 ppm (based upon lower body weight and reduced food consumption for both generations of the 1500 ppm treatment groups), **Reproductive NOEL**: 1500 ppm, **Developmental NOAEL**: 500 ppm (based upon severe reduction in body weight gain of pups in all 1500 ppm treatment litters during lactation period), **Developmental NOEL**: 100 ppm (based upon lower pup body weights of the F2B litters in the 500 ppm treatment group); **Study acceptable**. (Moore, 9/14/95)

#### TERATOLOGY, RAT

\*\* 028; 139806; "Developmental Toxicity Study of DPX-T3217-113 (Cymoxanil) in Rats", (L. Alvarez; E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE; Report No. 744-92; 1/25/93); Cymoxanil technical (purity: 97.8%); 25 females/group; Doses: 0, 10, 25, 75, 150 mg/kg, by gavage on days 7 through 16 of gestation; **Maternal**: no mortality; Clinical Observations: reduced mean body weight gain-days 7 thru 9 (75, 150 mg/kg/day), days 9 thru 11 (150 mg/kg/day), reduced food consumption-days 7 thru 13 (75, 150 mg/kg/day); Necropsy: no treatment-related lesions; **Developmental**: significantly reduced litter size due to increased incidence of early resorptions (150 mg/kg/day), reduced no. of male fetuses/litter (75, 150 mg/kg/day), increased no. of fetuses exhibiting retarded development resulting from a dose-related delay in ossification, but reduced mean fetal body weight detected in high dose group only (25, 75, 150 mg/kg/day); **No adverse effects**; **Maternal NOEL**: 25 mg/kg/day (based upon reduced body weight gain and reduced food consumption in 75 mg/kg/day treatment group); **Developmental NOEL**: 10 mg/kg/day (based on growth retardation in the 25 mg/kg/day group); **NOAEL** > 150 mg/kg/day; **Study acceptable**. (Moore, 9/12/95)

#### TERATOLOGY, RABBIT

\*\* **026, 027, 135; 139802, 139805, 159739**; "Teratogenicity Study of INT-3217 in New Zealand White Rabbits (Segment II Evaluation)", (E.L. Feussner; Argus Research Laboratories, Inc., Horsham, PA; Study No. 104-001; 7/1/82); Cymoxanil Technical (INT-3217-90, purity: 95.8%); 20 females/group, except for the control (17) and 1 mg/kg/day (18); Doses: 0 (vehicle: corn oil), 1, 4, 8, 32 mg/kg/day, by gavage, on days 6 thru 18 of gestation; **Maternal**: No treatment-related mortality, Clinical Observations: no treatment-related signs or effects upon body weights; Necropsy: no treatment-related lesions; **Developmental**: increased incidence of fetal malformations (cleft palate, rib alterations) (32 mg/kg/day); **Possible adverse effect**: increased incidence of fetal malformations; **Maternal NOEL** = 32 mg/kg/day; **Developmental NOEL** = 8 mg/kg/day (based upon increased incidence of malformations in fetuses of the 32 mg/kg/day

treatment group); Study initially unacceptable (Moore, 9/8/95) but upgraded to **acceptable** status with the submission of analytical data on the dosing material (Leung, 3/4/98).

101; 156100; "Effect of H12712 on Pregnancy of the New Zealand White Rabbit" (David D. Cozens, *et al*; Huntingdon Research Centre, Huntingdon, England; DuPont Report No. HLO 319-80; 4/14/80); H12712 (Batch No. 7800-20-C; 94.2% a.i.), dosed as suspensions in 1% methyl cellulose to groups of 15 mated female NZW rabbits at dose levels of 0 (vehicle), 4, 8, or 16 mg/kg/day on days 6-18 of gestation; 14 does died or were killed before study termination due to anorexia, abortion, or dosing accidents (distribution of unscheduled deaths was 5, 5, 3, and 1, from control to high-dose, respectively); these deaths were not considered treatment-related because the incidence was not dose-related; in addition, one doe in the high-dose group had a total litter loss (11 recently-deceased pups) at C-section on day 29; no compound-related toxicity was observed in does during gestation; no apparent effects on reproductive parameters were observed; malformed fetuses were found in 1/9, 0/8, 4/7, and 2/10 litters (control to high-dose, respectively); **Unacceptable** and cannot be upgraded because of the high incidence of mortality in the control, low-, and mid-dose groups. (Duncan, 10/31/97).

101; 156101; "Effect of H12712 on Pregnancy of the New Zealand White Rabbit" (Anthony K. Palmer, *et al*; Huntingdon Research Centre, Huntingdon, England; DuPont Report No. HLO 805-81; 11/13/81); H12712 (Batch No. 7800-20-C; 94.2% a.i.), dosed as suspensions in 1% methyl cellulose to groups of 15 mated female NZW rabbits at dose levels of 0 (vehicle), 8, 16, or 32 mg/kg/day on days 6-18 of gestation; clinical signs of cold ears, reduced food consumption or fecal output, and weight loss were observed in dams; reduced body weight gain was observed in the high-dose group; no effect on reproductive parameters was observed; an increase in the incidence of various defects of the axial skeleton ranging from the presence of cervical ribs to scoliosis was observed in fetuses in all dose groups compared to controls; **possible adverse effect**: malformations of upper axial skeleton; maternal NOEL = 16 mg/kg/day (reduced body weight gain); developmental NOEL < 8 mg/kg/day (skeletal defects observed at all dose levels); **Unacceptable** and cannot be upgraded because a NOEL for developmental effects was not established. (Duncan, 11/3/97).

#### GENE MUTATION

52067-030; 139836; mutagenicity; 842; "Mutagenicity Testing of DPX-T3217-113 (Cymoxanil) in the Salmonella typhimurium Plate Incorporation Assay" by V.L. Reynolds, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE; project ID #573-92; 9/18/92; test article a blend of lot #80317145 and #80321154; ~97% pure; because initial cytotoxicity test in strain TA100 indicated severe cytotoxicity -/+ S9 @ 2500 & 5000 ug/plate (less severe toxicity was also noted at 500 ug/plate -S9 and at 1000 ug/plate +S9), tester strains TA100, 1535, 97, & 98 (strains were confirmed concurrently w/each trial) were exposed to 0, 10, 50, 100, 250, 500, 750, 1000, & 2500 ug/plate for ~48 hr @ 37°C; triplicate plates, -/+ S9 microsomes, 2 separate trials; there were no increases in the # of histidine revertants in any tester strain -/+ S9 despite testing into the cytotoxic range for each strain and despite the functionality of the positive controls; DPX-T3217-113 is not mutagenic in the Ames assay under the present conditions; no adverse effects; **Acceptable**. (Rubin, 9/19/95)

52067-031; 139842; mutagenicity; 842; "Mutagenicity Evaluation of DPX-T3217-113 (Cymoxanil Technical) in the CHO/HPRT Assay" by V.L. Reynolds, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE; project ID #826-92; 5/24/93; test article a blend of lot #80317145 and #80321154; ~97% pure; dose range set by an initial cytotoxicity test which showed reductions in cell number/flask at the time of subculture at 0.5 mg/ml (-S9) and 1.5 mg/ml (+S9); doses, -S9 (19-20-hr incubation time, duplicate dishes, 2 trials): 0, .005, .01, .1, .25, .5, & .75 mg/ml; +S9 (5-hr exposure time, duplicate dishes, 2 trials): 0, .01, .05, .1, .25, .75, & 1.5 mg/ml; +S9 (third trial): .25, .5, .75, 1, 1.25, & 1.5 mg/ml; after exposure -S9 cells were replated immediately @ 200 cells/dish to assess toxicity and @ 106 cells/dish, subcultured 2x over the next week, and replated @ 2x10<sup>5</sup> cells/dish + 10<sup>-5</sup> M 6-thioguanine, incubated for 7-9 days, and the resistant (mutant) colonies counted; +S9 cells were incubated in

culture medium for 20-23 hr prior to subculture; despite some irregularities in the results, clear evidence for mutagenicity was not forthcoming from this study; positive controls (-S9, 62.6 mg/ml ethyl methane sulfonate; +S9, 3.9 mg/ml dimethyl benzanthracene) were functional; DPX-T3217-113 is not considered mutagenic in the CHO/HPRT assay under the present conditions; no adverse effects; **Acceptable.** (Rubin, 9/27/95)

### CHROMOSOME EFFECTS

52067-032; 139844; structural chromosome aberration; 843; "In vitro Evaluation of DPX-T3217-113 (Cymoxanil Technical) for Chromosome Aberrations in Human Lymphocytes" by D.L. Covell, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE; project ID #835-92; 2/10/93; test article a blend of lot #80317145 and #80321154; ~97% pure; 2 complete trials were run using a pair of male & female donors for each trial (1 replicate/sex at each concentration where possible); whole blood cultures were prepared from each donor; 3-4 hr exposure time; in cytotoxicity tests done +/- S9 microsomes, the avg. generation time increased at the 2 high concentrations (1.25 & 1.5 mg/ml), establishing the high dose for the aberration assays; doses chromosome aberration assays, Trial 1, +/- S9 microsomes: 0 (1% DMSO), 0.1, 0.5, 0.75, 1.0, 1.25, & 1.5 mg/ml; Trial 2, +/- S9: 0, 0.1, 0.85, 1.25, & 1.5 mg/ml; statistically significant increases in % cells w/≥ 1 aberration were observed in Trial 1, -S9 @ 1.5 mg/ml & +S9 @ 1, 1.25, & 1.5 mg/ml, and in Trial 2, -S9 @ 1.25 & 1.5 mg/ml & +S9 @ 0.85, 1.25, & 1.5 mg/ml; the majority of aberrations were gaps (excluded from the statistics) or chromatid breaks; statistically significant increases were not observed @ 0.75 mg/ml and below; positive controls were functional; DPX-T3217-113 is clastogenic in the human lymphocyte chromosome aberration assay under the present conditions; **adverse effect indicated; Acceptable.** (Rubin, 9/28/95)

52067-033; 139845; structural chromosome aberration; 843; "Mouse Bone Marrow Micronucleus Assay of DPX-T3217-113 (Cymoxanil Technical)" by K.M. Gerber, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE ; project ID #827-92; 3/10/93; DPX-T3217-113, a blend of lot #80317145 & #80321154 (~97% pure), administered by oral intubation to 5/sex/sacrifice time (except for 6 males/sacrifice time and 4 females/sacrifice time at the high dose) at 0 (15 ml water/kg), 125, 225, 350 (F only), or 450 (M only) mg/kg bw; bone marrow smears prepared @ ~24, 48, & 72 hr for control & high dose animals and @ ~24 hr for remainder; 5 high dose females were dead by 4 hr, with another dying by 24 hr (no male deaths); clinical signs (abnormal gait, lethargy, tremors, & ruffled fur) were noted w/i 1 hr in 16/18 high dose (HD) males, with the tremors subsiding by 3-5 hr, and ruffled fur the only evident sign by 24 hr; 17/18 HD females also exhibited clinical signs by 1 hr including exophthalmus, abnormal gait, lethargy, rapid or irregular respiration, tremors, and prostrate posture; lesser signs noted at lower doses; no statistically significant increase in micronucleated polychromatic erythrocytes was detected in any dose group at any sacrifice time; a statistically significant depression of the polychromatic/normochromatic ratio was noted in high dose females at the 48 hr sacrifice; DPX-T3217-113 did not induce micronuclei under the conditions tested; no adverse effects; **Acceptable.** (Rubin, 9/28/95)

### DNA DAMAGE

52067-034; 139847; other genetic effects; 844; "Assessment of DPX-T3217-113 (Cymoxanil Technical) in the In vitro Unscheduled DNA Synthesis [UDS] Assay in Primary Rat Hepatocytes" by K.S. Bentley, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE; project ID #796-92; 1/18/93; test article a blend of lot #80317145 and #80321154; ~97% pure; 2 complete trials; 0, 5, 10, 50, 100, 250, 500, 750, 1000, 1500 (Trial 2 only), & 2000 (Trial 1 only) ug/ml; 2000 ug/ml just exceeded the solubility limit; chamber slides were inoculated w/5x10<sup>5</sup> hepatocytes/chamber, duplicate cultures; after attachment, cultures were exposed to test article + 3H-thymidine for 18 hr; cytotoxicity, indicated by a rise in medium LDH, occurred in Trial 2 at & above 500 ug/ml; this was corroborated by a decrease in total cellular grains at those concentrations; autoradiography was performed to determine net nuclear grain counts (≥5 NNG indicative of UDS); statistically significant increases in UDS were noted in Trial 1 at 5, 10, 50, 100, 250, & 500 ug/ml, and in Trial 2 at 5, 10, 100, & 250

ug/ml; while a significant linear dose responsiveness was not found, the results are considered positive for UDS; positive controls (.02 and .2 ug/ml 2-AAF) were functional; DPX-T3217-113 induces UDS in rat hepatocytes; **adverse effect indicated; Acceptable.** (Rubin, 9/29/95)

52067-035, -102; 139848, 156102; other genetic effects; 844; "Determination of Unscheduled DNA Synthesis [UDS] in Rat Hepatocytes and Spermatocytes Following In vivo Exposure to DPX-T3217-113 [Cymoxanil Technical] by Oral Gavage" by K.S. Bentley, Haskell Laboratory for Toxicology and Industrial Medicine, E.I. du Pont de Nemours and Company, Newark, DE; project ID #169-94; 6/2/94; test article, a blend of lot #80317145 and #80321154 (~97% pure) administered by oral intubation to 5 males/dose/sacrifice time at 0 (10 ml 0.5% methylcellulose/kg), 500, or 1000 mg/kg bw; animals sacrificed @ 2 & 16 hr post dose and hepatocytes & spermatocytes isolated and cultured in the presence of 3H-thymidine (hepatocytes, 4 hr; spermatocytes, 24 hr) for autoradiographic determination of UDS; mortality and morbidity: 1-500 mg/kg rat died immediately upon exposure; by 16 hr, 3-1000 mg/kg rats were dead; clinical signs in both groups included prostrate posture, labored or rapid respiration, lethargy, tremors, diarrhea, & abnormal gait; cytotoxicity and UDS: DPX-T3217-113 did not induce cytotoxicity in hepatocytes (cell viability: 92.4-99.6%, comparable to controls) or spermatocytes (cell viability: 95-99% for both control and treated animals); UDS analysis did not yield any statistically significant increases or dose trends; no adverse effects; **Acceptable.** (Rubin, 10/2/95) Updated with references to rebuttal submitted to USEPA. (Duncan, 11/3/97)

### NEUROTOXICITY

\*\*52960-0030 207331, "Oral (Gavage) Developmental Neurotoxicity Study of Cymoxanil in CrI:CD<sup>®</sup> (SD)IGS BR VAF/Plus<sup>®</sup> Presumed Pregnant Rats", (Raymond G. York, Argus Research Laboratories, Inc., Horsham, PA., Report No. DuPont 3146, Project No. Argus 104-021, 9 February 2001). 25 CrI:CD<sup>®</sup> (SD)IGS BR VAF/Plus<sup>®</sup> mated females received Cymoxanil Technical (DPX-T3217) (97.2% cymoxanil) by oral gavage at 0 (0.5% aqueous methylcellulose), 5, 50, and 100 mg/kg/day on (presumed) gestation days 6 through lactation day 21 (post-partum) (rats that delivered a litter) or gestation day 24 (dams that did not deliver a litter). On post-partum day 12, pups were assigned to subsets for evaluation of behavior and development. One male pup and 1 female pup per litter per group were assigned to each of 5 subsets: Subset 1 (brain weights and neurohistology on lactation day 12); Subset 2 (passive avoidance, for learning, short-term retention, and hyperactivity) on post-partum days 24, 25, 31, and 32 and in a water maze, for overt coordination, swimming ability, learning and memory on days 59 to 61 and 66 to 68; Subset 3 (motor activity, movements of each pup were monitored by a passive infrared sensor mounted outside a stainless-steel cage) on post-partum days 14, 18, 22, and 60 and (auditory startle habituation, within a sound-attenuated chamber) on days 23 and 61; Subset 4 (ten animals/sex/group were sacrificed on each post-partum day from 80 to 83 for neurohistological examination following perfusion); and Subset 5 (pups were used to standardize litter size to eight pups per litter, they were necropsied on day 22). No treatment related deaths or clinical observations were noted for F0 dams. Bodyweight and food consumption were reduced (statistically significant) at 100 mg/kg/day during gestation and lactation. Statistically significant reductions in food consumption were also recorded at 50 mg/kg/day. Maternal NOEL = 5 mg/kg/day. No behavioral, gross, or microscopic evidence of treatment-related developmental neurotoxicity was noted in F1 animals. Differences in brain morphometrics in mid and high dose males (anterior-posterior lengths of cerebrum) and high dose females (cerebellar height) were noted relative to study controls but the biological significance was not determined. Means were within historical control ranges (measurement accuracy tolerances were considered as well). Decreases in pup survival (statistically significant), bodyweight, and bodyweight gain were recorded at 100 mg/kg/day. Extensive negative and positive control data for Argus were included in the report. Developmental NOEL = 50 mg/kg/day. No adverse effects. Acceptable. (Green and Gee, 2/5/04).

## SUBCHRONIC TOXICITY

(Oral)

**020 139834** "Subchronic Oral Toxicity: 90-Day Study with DPX-T3217-107 (Cymoxanil) Feeding and Neurotoxicity Study in Rats" (Malek, D. 821, E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware. Study HLR 370-91, 4/6/93). Cymoxanil, (lot # 107, purity of 97.6%) was given orally in the feed to 20 CrI:CD®BR rats /sex/dose (10 rats/sex/dose used for neurotoxicity subgroup) for 90 days at levels of 0, 100, 750, 1500 or 3000 ppm; Mortality: female (750 ppm level) found dead on day 42 (probably not dose-related); Body weight gain reduced in 1500 and 3000 ppm groups; Clinical pathology: Mean total leucocyte counts decreased in the 1500 and 3000 ppm groups at day 45 and 90; **NOEL (M) = 100 ppm** (based on testicular and epididymal histological changes), **(F) = 750 ppm** (reduced body weight); **Possible Adverse Effect [NOAEL (M) =100 ppm]:** increased elongate spermatid degeneration, **(F) = 3000** (no adverse effects reported); Neurotoxicity subgroup: **NOEL (neurotoxicity) (M) = 1500 ppm** (based on reduction in relative forelimb grip strength), **(F) = 3000 ppm** (no neurotoxic effects reported). **No Adverse Neurotoxic Effects reported. ACCEPTABLE;** Kellner, 10/4/95.

**021 139835** "Subchronic Oral Toxicity: 90-Day Study with DPX-T3217-107 Feeding Study in Mice" (Cox, L., 821, E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware. Du Pont Study HLR 630-91, 4/6/93). Cymoxanil, (lot # 107, purity of 96.9%) given orally in the feed to 10 CrI:CD®-1(ICR)BR mice/sex/dose for 90 days at levels of 0, 50, 500, 1750, 3500 or 7000 ppm; Mortality: moribundity and premature death resulted in termination of 7000 ppm groups in second and third weeks; body weight gain significantly reduced by 40, 47 and 56% in 500, 1750 or 3500 ppm males, respectively (day 0-98, p < 0.05); relative liver weights were significantly elevated in 1750 and 3000 ppm females without any abnormal histopathological changes; Clinical signs: increased pallor and hunched posture at 7000 ppm; **NOEL (M) = 50 ppm** (based on reduced body weight gain), **(F) = 500 ppm** (elevated relative liver weight); **Possible Adverse Effects [NOAEL(M/F) = 3500 ppm]:** Histopathology revealed pancreatic necrosis in 7/10 males and 7/10 females at 7000 ppm and cerebral hemorrhage in 4/10 females at 7000 ppm; **UNACCEPTABLE but possibly upgradeable** with submission of results from serum chemistry; Kellner, 10/11/95.

**022 139837** "Subchronic Oral Toxicity: 90-Day Study with DPX-T3217-113 (Cymoxanil) Feeding Study in Dogs" (Tompkins, E. 821, WIL Research Laboratories, Inc., Ashland, OH, Study HLO 797-92, 1/19/93). Cymoxanil, (lot # 113, purity of 97.8%) given orally in the feed to 4 beagle dogs/sex/dose for 13 weeks at levels of 0, 100, 200 and 250/500 ppm (increased to 500 ppm at week 2). Mortality: high-dose female (with dose-related symptoms) killed in extremis during week 10. Observations- decreased defecation (mid- and high-dose), diarrhea (mid- and high-dose males), dermal atonia/hypoactivity (high-dose); reduced body weight gain and food consumption in high dose animals; **NOEL (M/F) = 100 ppm** (based on clinical observations - see above); **Possible Adverse Effect [(NOAEL (M) = 200 ppm):** reduced testicular and epididymal weights and aspermatogenesis (high-dose), **(F) = 500** (no adverse effects reported); **ACCEPTABLE;** Kellner, 9/22/95.

(Dermal)

100; 156099; "Repeated Dose Dermal Toxicity: 28-Day Study with DPX-T3217-113 (Cymoxanil) in Rats" (Finlay, C., E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Haskell Laboratory Report No. 374-96, 9/10/94). 822. DPX-T3217-113 (Cymoxanil Technical) (Lot No. T3217-113, purity=97.8%), moistened with deionized water, was applied to the shaved skin of 5 CrI:CD®BR CD rats per sex per dose at concentrations of 0, 50, 500, or 1000 mg/kg/day for 6 hours for each of 28 consecutive days. One male at 500 mg/kg was killed accidentally. No treatment-related clinical signs were observed. No dose-related skin irritation was observed. No statistically significant hematologic changes were observed. No dose-related clinical chemistry changes were observed. Macroscopic and microscopic examination revealed no treatment-related abnormalities. **No adverse effects.** NOEL (systemic and dermal, M/F)=1000 mg/kg/day. **Acceptable.** (Corlett, 10/7/97)

## METABOLISM

52067-036; 139850; metabolism; 851; "The Absorption, Distribution, Metabolism and Excretion of [2-<sup>14</sup>C]-DPX-T3217 in the Rat" by L.J. Brown et al., Inveresk Research International, Tranent, Scotland; ID #2083-91; 10/28/94; 2.5 & 120 mg/kg in corn oil, 0.5 & 2 ml/animal, ~10 & ~20 uCi/animal, respectively; HD set by expectation of slight toxicity; single gavage administration: 3/sex/dose - blood pharmacokinetics, 5/sex/dose - elimination/distribution, 8/sex/dose - tissue distribution; multiple administration (cold dosing @ 2.5 mg/kg for 14 days followed by labeled dose): 5/sex; no significant differences between groups in blood/plasma and tissue residue profiles; max. blood concentrations were attained by 4 hr; with the possible exception of a somewhat decreased relative fecal excretion at the high dose (both sexes) and at the multiple low dose (males only), no significant differences in excretion time or route were seen when comparing sexes, doses, or single vs. multiple dosing regimes; including all dose groups, 57-65% of the administered dose (AD) recovered in urine & 5-17% in feces by 24 hr, 63-75% in urine & 16-24% in feces by 96 hr; @ 96 hr <1% of AD remained in tissues (highest levels found in kidney, liver, & skin); **Supplemental.** (Rubin, 9/14/95)

52067-037; 139856; metabolism; 851; "The Absorption, Distribution, Metabolism and Excretion of [2-<sup>14</sup>C]-DPX-T3217 in the Rat (Supplement #1)" by L.J. Brown et al., Inveresk Research International, Tranent, Scotland; ID #2083-91 (Suppl. #1); 1/5/95; main absorption, distribution, & excretion data reviewed in W139850.851; single dose groups: 2.5 & 120 mg/kg in corn oil, 0.5 & 2 ml/animal, ~10 & ~20 uCi/animal, groups D & E, respectively; multiple dose group: daily administration @ 2.5 mg/kg for 14 days followed by labeled dose @ 2.5 mg/kg, group F; 5/sex/dose regimen; the primary metabolites detected by HPLC and TLC in excreta were IN-W3595 (2-cyano-2-methoxyimino acetic acid) and polar components (glycine and other amino acid conjugates); group D, male, 24 hr: 58% of AD in urine (8.6% as IN-W3595, 46.5% as polars), 21.9% in feces (14% extractable, <1% IN-W3595, 13.1% polars); female: 64.2% of AD in urine (16.1% IN-W3595, 45.2% polars), 16.3% in feces (10.1% extractable, <1% IN-W3595, 8.7% polars); group E, male: 70.3% of AD in urine (26.3% IN-W3595, 40.3% polars), 16.1% in feces (11.3% extractable, <1% IN-W3595, 8.6% polars); female: 73% of AD in urine (33% IN-W3595, 36.7% polars), 17.1% in feces (11.5% extractable, <1% IN-W3595, 8.5% polars); group F, male: 66.2% of AD in urine (6.5% IN-W3595, 55% polars), 14.5% in feces (9% extractable, <1% IN-W3595, 8.9% polars); female: 63.1% of AD in urine (11.1% IN-W3595, 46.6% polars), 19.4% in feces (12.3% extractable, <1% IN-W3595, 12.2% polars); **Supplemental.** (Rubin, 9/15/95)

52067-038; 139858; metabolism; 851; "The Absorption, Distribution, Metabolism and Excretion of [2-<sup>14</sup>C]-DPX-T3217 in the Rat (Supplement #2)" by M.S. Prout & P.W. Lee, Inveresk Research International, Tranent, Scotland; project ID #2083-91 (Suppl. #2); 7/28/95; main absorption, distribution, & excretion data reviewed in W139850.851; study was designed to detect IN-U3204 (1-ethyl-5,6-di-2,4(1H,3H) pyridinedione), a possible cyclized intermediate in the pathway toward glycine, in urine; the most sensitive means found to detect IN-U3204 was liquid chromatography-mass spectrometry (LC-MS) using atmospheric pressure chemical ionisation (APCI) in the negative ion mode; IN-U3204 was detected in pooled 0-48 hr urine samples, both sexes, from animals treated with 120 mg/kg DPX-3217 (Group E, record #139850) and in pooled 0-24 hr samples, both sexes, from animals treated with 2.5 mg/kg in an ongoing low dose biliary fistula study; the latter group was included to ensure that the presence of IN-U3204 was not an artifact of storage; IN-U3204 was detected in both groups, though at apparently low levels; **Supplemental.** (Rubin, 9/18/95)

102; 156103; "Biliary Excretion of [<sup>14</sup>C]Cymoxanil in the Rat" (G. Y. McCorquodale and Martin S. Prout; Inveresk Research International, Tranent, Scotland; DuPont Report No. AMR 3326-95; 10/26/95); five SD rats/sex with cannulated bile ducts were dosed orally with 2.5 mg/kg of [<sup>14</sup>C]Cymoxanil (radiochemical purity = 98%; 14.09 uCi/mg) as a corn oil suspension; urine, feces, and bile were collected over a 48 h period, after which the animals were terminated and whole blood, liver, kidneys, and residual carcass were collected for measurement of radiolabel; previously characterized metabolites were measured in urine and bile; more than 85% of the test compound was eliminated in urine (~65%), feces (~14%), and bile (~7%) within 48 h in both

sexes, with most elimination occurring within the first 24 h; polar amino acid conjugates comprised the major class of metabolites found in both urine (~45-50%) and bile (~4-6%); Metabolite A (unknown) and IN-W3595 were found at much lower concentrations (< 10%) in urine; IN-W3595 was found at higher concentrations in the urine of females (7.7%) as compared to males (2.8%); Metabolite A was not found in bile; **Supplemental**. (Duncan, 10/31/97).

#### Summary

Cymoxanil is rapidly absorbed and maximum concentrations in the blood and plasma is reached within 4 hours after dosing. Rapid and almost complete elimination of the administered radioactive dose was observed in urine and feces within 48 hours. Excretion is primarily by urine (64 - 75%), fecal (16 - 24%) and expired air (< 5%) of the administered dose. There is no significant difference in residue profiles or elimination rates between sexes, dose levels, or single or multiple dosing. No evidence of bioaccumulation was detected. DPX-T3217 is metabolized extensively and only trace level of the administered [<sup>14</sup>C]-cymoxanil was detected in the urine and feces. IN-W3595 and glycine (and other amino acid conjugates) were detected as primary metabolites in the excreta. There were no significant differences in the metabolite distribution profile between sexes, high vs. low dose or single vs. multiple dosing regimen.